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PMSP/HSS
OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Follow-up to Methyl Bromide Registration Standard.
Amendment of 2/10/89. DEB Residue Data Requirements.
(DEB #5070)

FROM: Cynthia Deyrup, Ph.D., Chemist *C. Deyrup*
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THRU: Richard D. Schmitt, Ph.D., Acting Branch Chief
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TO: Jeffrey Kempter, Product Manager No. 32
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and

Toxicology Branch
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In this amendment, addressed to R. Tinsworth (RD), the registrant, the Methyl Bromide Industry Panel (MBIP), questions DEB's residue data requirements and contends that he can't proceed because of the Agency's constantly changing expectations. The registrant's complaints are addressed below.

Summary of Issues Addressed in Present Consideration

1. In the Methyl Bromide Registration Standard, DEB had requested storage stability data to cover the period from sampling to analysis, not just during the trip to the lab.

DEB is not concerned about the possible loss of MeBr residues from chilled samples over a 2-3 hour period, but if the sampling to analysis period approaches 10-12 hours, storage stability data will be needed.

2. If frozen samples are treated as described by the registrant, DEB is no longer concerned that MeBr may diffuse from samples before the determinative step.

If the registrant elects not to freeze the samples, he should describe the precautions taken to avoid loss of MeBr.

3. DEB has not required the registrant to determine the kinetics of desorption. This issue had only arisen because of difficulties in generating the residue data; DEB had pointed out that knowledge of the kinetics could enable the registrant to delete and/or shorten some experiments. Upon further reflection, DEB recommends that the validity of extrapolating 1st decline curves to the no-detect level should be checked if this approach is used.
4. Since it may take 3 months for MeBr residues to decline to the no-detect level in some commodities, processing studies are needed. This requirement was cited in the Registration Standard.

However, if the metabolism studies indicate that the only residue of concern is MeBr per se, DEB might consider waiving some of the studies on a case by case basis, especially if the processing involves heat. Such conclusions can only be drawn once the nature of the residue is adequately understood.

Present Consideration

I. MBIP, re: Storage Stability

MeBr is a gas and is very transient in foods. DEB is requiring data which are difficult to generate and which are "not very meaningful," such as storage stability of each commodity during shipping to the lab.

DEB is "preoccupied" with the fact that the reported residue levels may not reflect the levels which may be found by an FDA inspector.

DEB's Comments/Conclusions

The requirement for storage stability data to cover the period from sampling to analysis is not new.

The Residue Chemistry chapter of the Methyl Bromide Registration Standard (3/28/86) states, "...analyses must be conducted as soon as possible (perhaps within 12 hours) after sampling and/or samples must be stored in impermeable containers...To increase confidence in residue determinations, spiked samples of each crop should be handled just as the treated samples are to determine

the loss between treatment and analysis." Since tolerances are established to cover residues in commodities in interstate commerce, DEB considers it only logical that care should be taken to ensure that reported residue levels reflect those which an FDA inspector might find.

In a separate submission (dated 2/10/89), Dr. White states that samples would be analyzed as quickly as possible--in many cases, in less than 45 minutes--and the sampling to analysis period would be less than the time for the commodities to enter interstate commerce. He asks how residues can be determined earlier than "as soon as possible."

On December 16, 1988, members of DEB met with representatives of the MBIP (Dr. V. White and Dr. T. Duafala), Bolsa Labs (which is doing the analytical work), and the Dried Fruit and Tree Nut Association (DFA). Bolsa explained that samples would be analyzed within 2-3 hours of treatment and wanted to know whether it was necessary to freeze the samples for this short period.

DEB told them that freezing would probably not be necessary, as long as the samples were chilled. Mr. Preston Hartsell (USDA) had informed DEB at a meeting on 12/15/88 that freezing may actually disrupt cells and facilitate MeBr loss. DEB did not ask the registrant to measure MeBr losses incurred during the trip to the lab.

DEB is not concerned about the possible loss of MeBr residues from chilled samples over a 2-3 hour period, though samples should be cooled as quickly as possible to $<3.7^{\circ}\text{C}$, the boiling point of MeBr, and should be stored in impermeable containers. However, if the sampling to analysis time approaches 10-12 hours (or 24 hours, as in the registrant's previous submission), storage stability data for residues of MeBr would then be needed.

II. MBIP, re: Sample maceration

The registrant doesn't believe that the details of sample preparation (maceration/chopping) constitute "meaningful" information.

DEB's Comments/Conclusions

DEB did not ask for a description of sample maceration in the Registration Standard, but cannot agree with the registrant that such information is "not very meaningful." MeBr is a gas at room temperature, and the methodology called for the sample to be chopped or macerated. DEB therefore considered it reasonable to ask whether precautions had been taken to avoid loss of the gaseous analyte.

In a separate submission (also dated 2/10/89), the registrant explains that samples are received frozen, are fractured with a mallet, and are quickly subdivided into blending jars for

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analysis.

That is what DEB wanted to know. DEB is no longer concerned that MeBr may diffuse from samples before the determinative step, if the samples are handled as described above.

If the registrant elects not to freeze (see Issue I), he should describe the precautions taken to avoid loss of MeBr. In meetings with the registrant, DEB has explained that problems have arisen during this step with other volatile pesticides.

III. MBIP, re: Kinetics of Desorption

DEB is requiring data on the kinetics of desorption.

DEB's Comments/Conclusions

The kinetics of desorption were discussed at the meeting of 12/15/88. DEB is not requiring that the kinetics of desorption be delineated and regrets any misunderstanding that may have arisen.

This issue arose because the Residue Chemistry chapter of the Methyl Bromide Registration Standard had specified for many crops that aeration should continue until MeBr residues were undetectable (<0.001 ppm, if possible) and that the aeration should reflect commercial practices. DEB learned that it could take 3 months for some commodities (such as nuts) to decline to the undetectable level; if the decline studies could not be terminated before the no-detect level, the users said that it would take forever to generate the residue data. Also, aeration temperatures are not always controlled. In order to aid the registrant, DEB pointed out that if the decline curves obeyed first order kinetics, as reported in the literature for some commodities, it would be a simple matter to determine the first order rate constant. Once the rate constant is known, the time needed for MeBr residues to decline to an acceptable level at any temperature could be calculated from the first order rate expression, provided that first order kinetics prevail throughout the decline of MeBr.

Generally DEB prefers to see data reflecting both the worst case scenario and common commercial practice. DEB had suggested extrapolation from kinetic data only because of the problems discussed above.

Upon further reflection, if this approach is followed, DEB recommends that the validity of extrapolating first order decline curves to the no-detect level should be checked by allowing at least one study for each crop to continue to the no-detect level. Extrapolation from initial decline rates to the no-detect level may not be valid if other reactions of MeBr (besides desorption) become predominant at low MeBr levels.

At low levels of MeBr, the decline of MeBr could actually be

faster than would be predicted by first order kinetics. If that is the case, the registrant, extrapolating on the basis of first order kinetics, could be burdened by a prolonged and unnecessary aeration period.

IV. MBIP, re: Processing Studies

The registrant argues that MeBr residues are so transitory that DEB is concerned about loss from frozen containers in glass. How can residues survive processing?

DEB's Comments/Conclusions

The requirement for processing studies is not new. For instance, the Registration Standard cites the need for fractionation studies for the cereal grains, apples, tomatoes, etc.

The registrant is correct in describing MeBr residues as transitory. However, the rate at which MeBr levels decline depends upon the commodity. As mentioned above, it may take 3 months for MeBr residues to decline to the no-detect level in nuts.

However, if the metabolism studies indicate that the only residue of concern is MeBr per se, DEB might consider waiving some of the studies on a case by case basis. For instance, since the processing of some commodities involves elevated temperatures, residue data on molasses, refined oil, and dry pomace may not be needed. Such conclusions can only be drawn once the nature of the residue is adequately understood.

Other Considerations

The registrant has attached some of his responses to the amendment addressed to R. Tinsworth. These responses have also been submitted for review under separate cover and will be discussed in detail in other memoranda.

cc: A. Lindsay (RD)
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